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**Scharschmidt**

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(54) **METHODS OF TREATMENT USING AMMONIA-SCAVENGING DRUGS**

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(52) **U.S. Cl.**  
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(58) **Field of Classification Search**  
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See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

4,284,647	A	8/1981	Brusilow et al.	
5,968,979	A	10/1999	Brusilow	
6,060,510	A	5/2000	Brusilow	
6,083,984	A *	7/2000	Brusilow	514/533
6,219,567	B1	4/2001	Eggers et al.	
2004/0229948	A1	11/2004	Summar et al.	
2006/0135612	A1	6/2006	Ferrante	
2008/0119554	A1	5/2008	Jalan et al.	
2010/0008859	A1	1/2010	Scharschmidt	

**FOREIGN PATENT DOCUMENTS**

WO	WO-2005/053607	6/2005
WO	WO-2006/056794	6/2006
WO	WO-2009/087474	7/2009
WO	WO-2009/134460	A1 11/2009
WO	WO-2010/250303	A1 3/2010

**OTHER PUBLICATIONS**

Berry et al., *J Pediatrics* (2001) 138:S56-S61.  
 Brusilow, *Pediatric Research* (1991) 29:147-150.  
 Brusilow, *Progress in Liver Diseases* (1995) 12:293-309.  
 Brusilow and Finkelstein, *J Metabolism* (1993) 42:1336-1339.  
 Chang et al., *PNAS USA* (2001) 98(17):9808-9813.  
 FDA Label for Buphenyl, 6 pages.  
 Kasumov et al., *Drug Metabolism and Disposition* (2004) 32(1):10-19.  
 Rudman et al., *J Clin Invest* (1973) 52:2241-2249.  
 Singh, *Suppl to J Pediatrics* (2001) 138(1):S1-S5.  
 Thibault et al., *Cancer* (1995) 75(12):2932-2938.  
 Thibault et al., *Cancer Research* (1994) 54(7):1690-1694.

International Search Report and Written Opinion for PCT/US09/30362, mailed Mar. 2, 2009, 8 pages.  
 ClinicalTrials.Gov/Archive View of NCT00551200 on Dec. 11, 2007 "Dose-Escalation Safety Study of Glyceryl Tri (4-Phenylbutyrate)(GT4P) to Treat Urea Cycle Disorders" [accessed Oct. 5, 2009], 4 pages.

Comte et al., *Journal of Mass Spectrometry* (2002) 37(6):581-590.  
 Lee et al., *Journal of Inherited Metabolic Disease* (2008) 31(1):91.  
 Search and Examination Report for British Patent Application No. GB 0915545.8, dated Oct. 8, 2009, 5 pages.  
 MacArthur et al. (2004). *Molecular Genetics and Metabolism* 81(1):S67-S73.  
 Simmell et al. (1986). *Pediatric Research* 20(11):1117-1121.  
 Tanner et al. (2007). *Journal of Inherited Metabolic Disease* 30(5):716-721.

International Search Report and Written Opinion for PCT/US2009/055256, mailed Dec. 30, 2009, 13 pages.

Ambrose, A.M. et al. (1933). "Further Studies on the Detoxification of Phenylacetic Acid." *J. Biol. Chem.* 101:669-675.  
 Batshaw M.L. et al. (Dec. 1980). "Treatment of Hyperammonemic Coma Caused by Inborn Errors of Urea Synthesis," *J. Pediatr.* 97(6):893-900.

Batshaw, M.L. et al. (Aug. 1981). "New Approaches to the Diagnosis and Treatment of Inborn Errors of Urea Synthesis," *Pediatrics* 68(2):290-297.

Batshaw M.L. et al. (Jun. 10, 1982). "Treatment of Inborn Errors of Urea Synthesis: Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion," *N. Engl. J. Med.* 306(23):1387-1392.  
 Batshaw, M.L. (1984). "Hyperammonemia," in *Current Problems in Pediatrics*, Lockhart, J.D. ed.: Year Book Medical Publishers, pp. 2-69.

Brusilow, S.W. et al. (Sep. 1, 1979). "New Pathways of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Lancet* 2(8140):452-454.

Brusilow, S. et al. (Feb. 8, 1980). "Amino Acid Acylation: A Mechanism of Nitrogen Excretion in Inborn Errors of Urea Synthesis," *Science* 207:659-661.

Brusilow, S.W. (Jun. 21, 1984). "Treatment of Episodic Hyperammonemia in Children With Inborn Errors of Urea Synthesis," *N. Engl. J. Med.* 310(25):1630-1634.

Brusilow, S.W. et al. (1991). "Treatment of Urea Cycle Disorders," Chapter 5 in *Treatment of Genetic Diseases*, Desnik, R.J. et al. eds, Churchill Livingstone, New York, New York, pp. 79-94.

(Continued)

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(57) **ABSTRACT**

The invention provides a method for determining a dose and schedule and making dose adjustments of PBA prodrugs used to treat nitrogen retention states, or ammonia accumulation disorders, by measuring urinary excretion of phenylacetylglutamine and/or total urinary nitrogen. The invention provides methods to select an appropriate dosage of a PBA prodrug based on the patient's dietary protein intake, or based on previous treatments administered to the patient. The methods are applicable to selecting or modifying a dosing regimen for a subject receiving an orally administered ammonia scavenging drug.